Expression of SOX11 in Mantle Cell Lymphoma is Associated with Increased Angiogenesis and Immunosuppressive Microenvironment

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Disclosure

No conflicts of interests to disclose
Microenvironment in mantle cell lymphoma

Adapted from Papin A et al, Leuk Lymphoma. 2017
Balsas et al, Blood. 2017
Palomero J. et al, Blood. 2014

- Regulatory T-cells
- Immunosuppression
- Clinical significance
- Angiogenesis
Aims:

- To evaluate the **angiogenesis** by **immunohistochemistry** in a series of 56 nodal and splenic mantle cell lymphoma cases

- To characterize the **immune cell infiltrate** by **immunohistochemistry** and **gene expression profiling** in a series of 51 nodal mantle cell lymphoma cases

- To correlate with SOX11 expression and outcome
Methods: Angiogenesis

**Microvascular density (MVD):** Number of intratumoral microvessels/μm²

**Microvascular area (MVA):** the sum of all microvascular areas (μm²) divided by the total area of the tissue (μm²)

**CD34 (IHC):** 10 intratumoral areas

SOX11+: N=27
SOX11-: N=3

SOX11+: N=8
SOX11-: N=15

SOX11+: N=3

**FFPE**
Analysis Imaging Software for Life Sciences Microscopy

Petrakis, Veloz et al, Histopathology. 2019
Methods: Immune cell microenvironment

Lymph nodes (N=51)
- SOX11+: N=43
- SOX11-: N=8

IHC
- TILs
  - CD3
  - CD4
  - CD8
  - Granzyme B

- T regs
  - FOXP3
  - CTLA4

- TAMs
  - CD68
  - CD163

Tumor cells
- CD70 (CD27L)

CD70
- Tumor cell
  - CD70
  - CD27

FOXP3 eTregs
  - CTLA-4
Methods: Immune cell microenvironment

Gene expression profiling

Lymph nodes (N=20)

SOX11+: N=11
SOX11-: N=3
RH: N=6

Immune panel of Nanostring®

FFPE
80-85% tumor cell content

770 genes related to immune response
Results: SOX11-positive MCL show increased vascularity

<table>
<thead>
<tr>
<th>SOX11+</th>
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<td>CD34</td>
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**Results:** SOX11-positive MCL show increased vascularity.

**MVA:** $14.5 \times 10^{-3}$ vs $5.0 \times 10^{-3}$, $p<0.001$

**MVD:** $18.6/\mu m^2$ vs $14.2/\mu m^2$, $p=0.021$

Petrakis, Veloza et al, Histopathology. 2019
Results: Increased angiogenesis is associated with a shorter overall survival

Petrakis, Veloza et al, Histopathology. 2019
Results: SOX11 expression is associated with decreased CD3+ and CD4+ TILs.
Results: MCL show a differential expression of immunity related genes according to SOX11 expression.
Results: Expression of immunity related genes have clinical impact on outcome in MCL

**T CELLS SCORE**

HR=0.55, p=5e-04

**CYTOTOXIC CELLS SCORE**

HR=0.48, p=1e-04
Results: SOX11 expression is associated with increased Tregs with impact on prognosis.

SOX11+ MCL

SOX11- MCL

FOXP3

FOXP3/CTLA4

IHC

GEP

HR = 52.741, p = 0.0216

HR = 16.112, p = 0.0024

High

Low

High

HR = 52.741, p = 0.0216

HR = 16.112, p = 0.0024
Results: MCL show a differential expression of immune related genes according to SOX11 expression.
Results: MCL show a differential expression of immune related genes according to SOX11 expression

SOX11+ vs. SOX11-

26 (32.5%)

24 (30%)

30 (37.5%)

SOX11+ vs. NRLN

MCL                      NRLN

CD70 RNA expression

Pearson r = 0.6141
P value = ** 0.0067
N = 17

HR = 1.37, p = 0.015

Low CD70

High CD70
Results: MCL show a differential expression of immune related genes according to SOX11 expression.
Results: Expression of immune related genes have clinical impact on outcome in MCL
Conclusions

• SOX11 expression in MCL is associated with increased angiogenesis and immunosuppression
• Angiogenesis and immunosuppression represent important **prognostic biomarkers** in MCL

• The evaluation of the microenvironment in MCL may help to stratify patients for targeted therapies

• Targeting the microenvironment (**anti-CD70, anti-CTLA4, anti-CSF1R**) and blood vessels (**antiangiogenics**) may be an effective approach in aggressive relapse/refractory MCL
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